Feature Article

The Front Line in Osteoporosis Diagnosis

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1. Introduction

Osteoporosis diagnosis requires a noninvasive method of estimating bone strength, and bone strength evaluation is particularly essential to diagnose osteoporosis and start treatment before fractures occur. Bone mineral density measured by dual-energy X-ray absorptiometry (DXA) is currently used as an indicator of bone strength. However, the reduced bone strength in osteoporosis is defined not only by reduced bone mineral density but also by factors collectively called “bone quality” such as bone geometry, microarchitecture, microfractures, metabolic turnover, and degree of bone calcification (Fig. 1). Here we briefly describe current methods of evaluating bone strength used in clinical practice including measurement of bone mass.

Bone strength = Bone mineral density + Bone quality (structure and material quality)

Bone microarchitecture
Bone metabolic turnover
Microfracture
Bone calcification

Fig.1 The effect of bone mineral density and bone quality on bone strength
Although bone mineral density accounts for around 70% of bone strength, the effects of other factors cannot be ignored.

2. Clinical Methods of Bone Strength Evaluation and Characteristic Features

2.1 Bone Mineral Density Measurement

Bone density, which is said to determine as much as 70% of bone strength, is obtained by bone mass measurement. Some methods of measuring bone mass include DXA by X-rays, quantitative CT (QCT), radiographic absorptiometry (RA), and quantitative ultrasound (QUS) by ultrasonography. RA and QUS can both measure bone mass in peripheral bones (RA: metacarpus, QUS: calcaneus, forearm bone, etc.) while DXA and QCT can measure bone mass in peripheral bones as well as the lumbar spine and the proximal femur. All of these are established methods of measuring bone mass that are still seeing improvements in accuracy and convenience.

2.2 Evaluation of Macroscopic Bone Morphology

Methods of evaluating bone morphology have long been considered in terms of the relationship between morphological measurements and risk of proximal femoral fracture. Femoral neck-shaft angle and neck length (hip axis length, HAL) correspond to the methods. Recently, the method to quantify the cross-sectional shape of the proximal femur (hip structure analysis, HSA) has been developed and is utilized as a tool in clinical research and in clinical trials to evaluate bone strength in the proximal femur in terms of structure (Fig. 2). HSA provides indexes shown in Table 1 at the three sites of the femoral neck, the intertrochanter, and the femoral shaft, and these show slightly different patterns of aging-associated and osteoporosis treatment-associated change compared to bone mineral

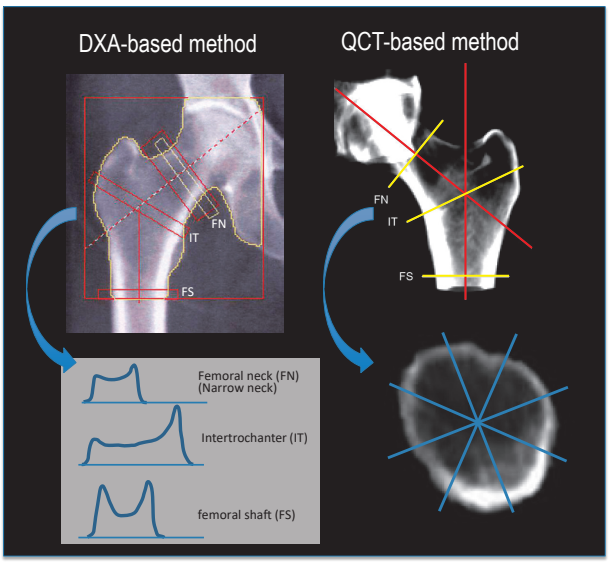

Fig.2 Strength analysis of the proximal femur (HSA) by CT and DXA.

density. Though the QCT-based method is more accurate, bone morphology can also be calculated based on the measurement data by DXA of the proximal femur.

Table 1. Indicators obtained by HSA

Bone outer diameter and cortical bone inner diameter
Mean cortical bone thickness
Bone cross-sectional area (area taken up by cortical and cancellous bone)
Second moment of area
Section modulus (indicator of strength against bending)
Buckling ratio (indicator related to strength against buckling)

2.3 Evaluation of Bone Microarchitecture

Bone structure imaging and analysis require image resolutions high enough for the intended application. For example, an image resolution of around 1 mm can be used to observe the shape of large bones, but an image resolution of around 100 μm is needed to observe the distribution of bone trabeculae.

Recent clinical CT can achieve image resolutions with a pixel diameter of 200 μm and a slice thickness of around 500 μm. Bone trabeculae width cannot be measured directly at this resolution, but bone microarchitecture can be evaluated quantitatively based on the distribution of cancellous trabeculae. For peripheral bones, high resolution peripheral quantitative CT (HR-pQCT), that is capable of an image resolution and slice thickness of 100 μm or less, is commercially available and used for quantitative evaluation of bone microarchitecture for cortical bone porosity and other characteristics.

Analytical software has been developed that calculates an indicator of cancellous bone structure (trabecular bone score, TBS) based on DXA scanning data. This software provides a simple method of evaluating cancellous bone structure and is currently being developed for clinical use (Fig. 3). TBS is a numerical indicator that is calculated based on the texture analysis of lumbar spine DXA images, and though this indicator has some limitations, it has attracted interests as a simple method of obtaining an indicator that correlates with cancellous bone microarchitecture.

2.4 Finite Element Analysis

Bone mass increases and decreases differently based on sites and localized factors such as stress risers at sites of reduced bone mass affect fracture occurrence. For this reason, fracture risk is determined based on a combination of bone strength and external force. Evaluations of fracture risk must therefore consider the size of the load on the bone as well as the site and direction of that load. Finite element analysis based on CT data (CT-FEM) creates a three-dimensional bone model from CT images of lumbar vertebrae or the proximal femur and predicts fracture risk based on sites where fractures start to occur when loading is increased under given conditions of mechanical loading and constraint, as well as based on the quantitative load when fracture starts to occur (Fig. 4). While CT image resolution is limited by the relationship between resolution and CT exposure dose, high-resolution data enables the acquisition and analysis of information on the microarchitecture of cancellous trabeculae.

2.5 Methods Other than Diagnostic Imaging

Apart from image-based diagnosis, other methods are being explored that are using blood and urine markers and measuring bone strength by microindentation.

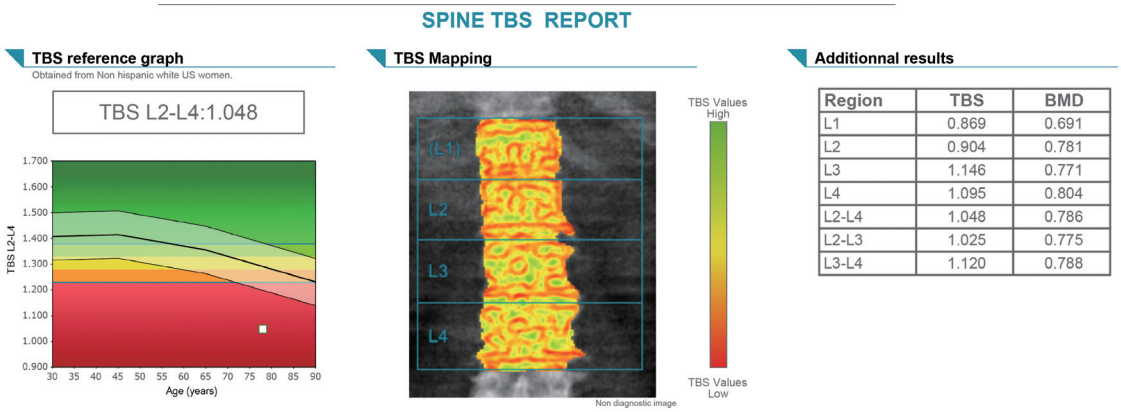

Fig.3 Evaluation of lumbar spine cancellous bone by DXA (TBS)
Results of analysis in a 78-year-old woman. Although L2–L4 BMD is still in the low bone mass range at 0.786 g/cm^2 (78 % of young adult mean, -1.9 T-score), TBS is markedly low at 1.048.

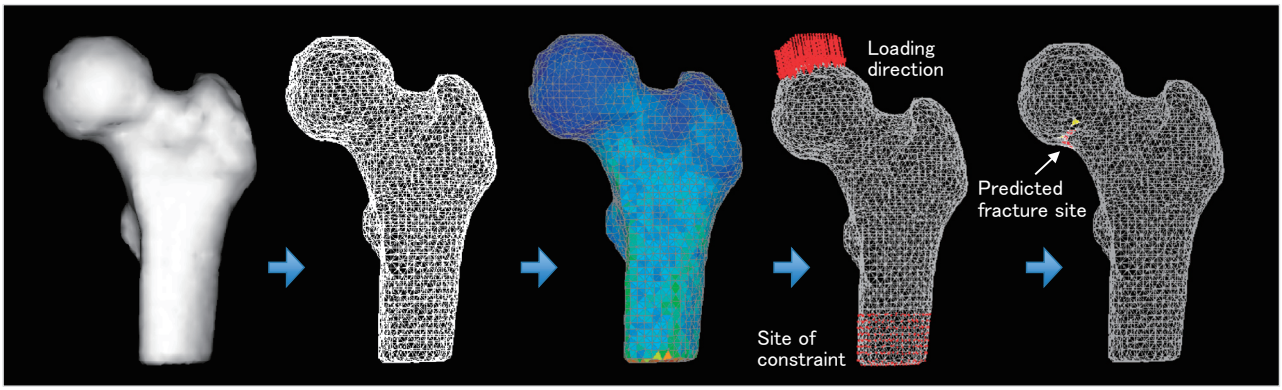

Fig.4 Predicting fracture loading by CT-FEM
Finite element analysis of CT data predicts fracture loading and fracture sites under given conditions of mechanical loading and constraint.

3. What Did New Methods Reveal?

3.1 Confirming the Utility of DXA-BMD as an Indicator of Bone Strength

One of the shortcomings of bone mass measurement by DXA is that bone mineral density is given in terms of unit surface area (areal bone mineral density, aBMD) and not unit volume. When two bones have identical volumetric bone mineral density (vBMD) but differ in size, the bigger bone will have a larger aBMD. This is considered to be the main reason that males have a larger aBMD than females. By contrast, epidemiological investigation has shown there is almost no sex-based difference in the relationship between DXA-based aBMD and fracture risk. Assuming a direct relationship between fracture risk and bone strength, the relationship between aBMD and bone strength should be almost identical in males and females.

According to a report using QCT of the proximal femur to investigate this relationship, aBMD is almost the same in males and females due to the fact that though males have larger bones than females, this size difference is balanced out by the smaller vBMD in males.[1] In addition, when calculated by CT-FEM, there is almost no sex-based difference in either bone strength or load-to-strength ratio (the ratio of strength to estimated load during a fall). CT-FEM-based investigations indicated that DXA-based bone density has become more significant as an index of bone strength as it contains the information of bone size.

3.2 Clinical Significance of Bone Geometry Indicators

Among the structural indices of the proximal femur, HAL is a different risk factor from bone mineral density of the proximal femur fracture. However, while HAL is used in epidemiological investigations of ethnic differences in fracture frequency, it is not used in osteoporosis to determine targets for therapeutic intervention.

HSA index was initially expected to be a clinical index that complements bone mineral density because of its association with fracture risk and its response to drug therapy. However, some HSA indicators, that are section modulus and buckling ratio in particular, are significant predictors of fracture but mainly used in clinical research because they are not so independent of bone mineral density and are also inferior to bone mineral density in terms of measurement reproducibility.

3.3 Age-Related Increase in Cortical Bone Porosity

Age is a risk factor for fracture that is independent of bone mineral density, but it has so far been difficult to observe differences in bone microarchitecture between young and elderly people who have equivalent bone mineral density in a clinical setting. According to findings from studies using HR-pQCT, among the indicators of cancellous bone microarchitecture such as trabecular width, trabecular number, cortical bone thickness and its porosity, cortical bone porosity particularly exhibits age-related changes that are independent of bone mineral density and suggests a relationship between lowering bone strength in the elderly.[2] In other words, though deterioration of bone

microarchitecture and decrease in bone mineral density progress with age, it's considered that the age-related changes of microarchitecture in cortical bone may be tending to be more independent of bone mineral density than the one in cancellous bone.

3.4 Utility and Limitations of Trabecular Bone Score (TBS)

Many study results have shown that TBS predicts fractures independent of bone mineral density in postmenopausal women. Also, incorporating TBS into FRAX® (WHO tool for evaluating fracture risk) increases the ability of FRAX® to predict fractures. For these reasons, TBS can be used to determine when to start drug treatment and expected to be helpful particularly for women near the therapeutic threshold according to existing standards and for women who are 65 years and younger.

A reduction in TBS is even seen in a variety of cases of secondary osteoporosis. Bone quality is generally considered to be a greater influence on reduction of bone strength in diabetes-induced and steroid-induced osteoporosis than in primary osteoporosis, and TBS is shown to be an effective indicator for evaluating bone strength in patients with these diseases.

The percentage change in TBS caused by osteoclastic inhibitors tends to be smaller than the one in bone mineral density, and the connection between fracture prevention and treatment-induced percentage change in TBS is also weaker than for bone mineral density. Consequently, TBS is not so suitable for evaluating the therapeutic effect of bisphosphonate and other osteoclastic inhibitors. As yet, no consensus has been reached on the change in TBS caused by agents that stimulate bone formation such as parathyroid hormone (PTH) or on the significance of such changes.

3.5 Clinical Significance of CT-FEM

CT-FEM is often considered the gold standard for clinical evaluation of bone strength and is used to analyze the detailed effects of drug treatment among other applications. For example, Keaveny et al. administered alendronate or teriparatide to patients with osteoporosis for 18 months then compared therapeutic effect by spine QCT.[3] Both alendronate and teriparatide increased vBMD and bone strength, but a larger percentage increase in vBMD and bone strength was observed with teriparatide than alendronate and there was a marked increase in cancellous bone with teriparatide. Furthermore, the percentage increase in bone strength/vBMD ratio was five times larger with teriparatide than alendronate and teriparatide was considered to be an effective means for increasing bone strength since it increases bone in the position which is important for the strength.

The general evaluation for the accuracy of CT-FEM is high, and International Society for Clinical Densitometry officially states that the ability of CT-FEM to predict vertebral body fractures is superior to bone mineral density determined by DXA, and the ability of CT-FEM to predict proximal femoral fractures is equivalent or better than bone mineral density determined by DXA.[4]

4. Conclusion

This article has described the current situation regarding methods of evaluating bone strength, which is an essential evaluating indicator in osteoporosis diagnosis. We look forward to these methods being utilized for pathological analysis of bone diseases, evaluation of fracture risk, and determining the therapeutic effect of drugs.

References

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